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AF/1644

Attorney Docket No. 018733/0967

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: David M. GOLDENBERG *et al.*

Title: IMMUNOTHERAPY OF AUTOIMMUNE DISORDERS USING ANTIBODIES WHICH TARGET B-CELLS

Appl. No.: 09/590,284

Filing Date: June 9, 2000

Examiner: J. Roark

Art Unit: 1644

REQUEST FOR RECONSIDERATION UNDER 37 CFR §1.116

Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the communication dated April 4, 2003, applicants request that the above-identified application be reconsidered in light of the remarks that follow.

Claims 1-5, 7, 12-15, 37 and 38 are pending. Claims 6, 8-11, and 16-36 are withdrawn from consideration as directed to a non-elected species. Upon allowance of a generic claim, these claims should be examined in the present case. Claims 1-5, 7, 12-15, 37 and 38 are rejected. Claims 1-5, 7, 12-15, 37 and 38 remain in the case.

Claim 5 is rejected under the first paragraph of Section 112. According to the examiner, the LL2 antibody must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. Forwarded with this response are papers evidencing a deposit of the LL2 antibody that has been made in another of the assignee's cases, which inadvertently was missing from applicant's previous submission. Withdrawal of the rejection of claim 5 is respectfully requested.

The rejection of claims 1, 2, 4, 7 and 14 under Section 102(e) based on Aruffo *et al.* (U.S. 6,051,228) has been withdrawn. The rejection of claims 1-4, 7, 12-15, 37 and 38 under Section 103(a) based on the combined teachings of Aruffo *et al.*, Meyer *et al.*, Anderson *et al.*, Tedder *et al.*, and The Merck Manual of Diagnosis and Therapy has been maintained. Claim 5 is rejected on the same references taken in view of Leung *et al.*

The examiner maintains that

> Aruffo *et al.* teach that CD40 is a B cell determiniant expressed on B cells (*e.g.*, column 1 at lines 25-31) and that antibody to CD40 depletes B cells when administered *in vivo* (*e.g.*, column 9 at lines 46 and column 12 at lines 37-55)...As noted *supra*, CD40 is a B cell antigen because although it is not expressed solely on B cells (*i.e.*, the Examiner acknowledges that CD40 is expressed on other cells, as taught by Aruffo *et al.* at column , lines 14-40), CD40 is expressed on B cells and therefore meets the limitation "a B cell antigen" as previously recited.

The examiner's rejection based on Aruffo *et al.* hinges on this characterization that the term "B cell antigen" denotes any antigen that is expressed on a B cell, regardless of the level of expression or whether that antigen is expressed on cells other than B cells. Yet even Aruffo itself highlights a distinction between "B cell antigens" and CD40, noting that CD40

> though ***originally*** identified as a B cell antigen, CD40 is ***now*** believed to be expressed by all antigen presenting cells (APC), including dendritic cells, keratinocytes, and monocytes. CD40 is also express by cell types that can act as APC under certain conditions, such as vascular endothelial cells, or cells involved in direct interactions with T cells or T cell precursors such as thymic epithelial cells. More recently, it has also been reported that CD40 can be expressed by fibroblasts, eosinophils, and activated T cells. CD40 expression has also been seen in cancerous cells.
> Emphasis added.

Moreover, the present claims recite more than just "B cell antigen." They recite the necessary presence of an antibody to a B cell antigen selected from the group consisting of CD22, CD20 and CD19. These three antigens, in contrast to CD40, are all antigens for

which the main reactivity is cells of B lineage, and can be used as B cell markers. The examiner has rejected applicants' previous proffer of evidence probative of this fact (http://www.biocarta.com/pathfiles/h_asbcellPathway.asp). Accordingly, applicants are forwarding with this response extensive references to establish that CD22, CD20 and CD19 are B cell markers, in clear contrast to CD40 disclosed by Aruffo. As such, a skilled artisan would not have been motivated to substitute antibodies to any of CD22, CD20, or CD19 for the CD40 antibody disclosed in Aruffo *et al.*

Probably the most extensively used marker to obtain a cell population of just B cells is CD19, despite the fact that it also may be found on a very small number of dendritic cells, which likely are derived from early B-lymphocytes. Thus, "CD Antigens in the B cell Section" (http://phoenix.jr2.x.ac.uk/BcellWork/sect.html) discloses that, although CD19 has some reactivity with follicular dendritic cells, its main cellular reactivity is "B lineage, from earliest recognisable B-lineage cells to B cell blasts, lost on maturation to plasma cells." Thus, it is taught as having application as a "marker for B lineage cells in leukaemia and lymphoma. Good pan-B marker in lymphocyte phenotyping." Pezzuto *et al.*, *Immunology* (1987) notes that "the 95 Kd CD19 antigen is the broadest lineage specific surface marker for B cells; it is present on the surface of virtually all B lymphocytes, including early B progenitor cells." A similar characterization is found in "Leukemia: Laboratory Evaluation – Immunophenotype" which notes that CD19 is the earliest B specific protein expressed on B cells" and "you should recognize CD19 as a pan B marker." Zhou *et al.*, *Mol. Cell Biol.* (1994) state that "CD19 is a B-cell specific member of the immunoglobulin superfamily." "Lymphocyte Typing" from The Royal College of Pathologists of Australasia; Crucian *et al.*, *Clin. Diagn. Lab Immunol.* (1995); and Rossi *et al.*, *Blood* (2002) all reference the use of anti-CD19 antibodies to quantify B cell subsets of cell populations.

Both CD20 and CD22 also are excellent B cell markers, being expressed only on B cells. "CD Antigens in the B cell Section," *supra*, discloses that the main cellular reactivity of CD20 is "B cells, from the pre-B stage to B cell blasts; lost on differentiation to plasma cells." Other reactive cells for CD20 also are B lineage specific. Use as a B lineage

marker is listed as an application of CD20, although CD19 is noted as being generally preferred. In similar fashion, CD22 is taught as having a main cellular reactivity of "B lineage" with no other cell reactivity. Likewise, "Cluster Designation Marker System" (http://www.keratin.com/am/am025.shtml) discloses that CD20 is expressed on B cells and CD22 is expressed on mature B cells. The B cell lineage reactivity of CD20 and CD22 is also mentioned in The Online Medical Dictionary, which defines CD20 as "unglycosylated phosphoproteins expressed only on B-cells" (http://cancerweb.ncl.ac.uk/cgi-bin/omd?CD20), and Stedman's Medical Dictionary, which defines CD22 as "a type I transmembrane protein found in the cytoplasm of pre-B cells and on the surface of mature B cells" (http://216.252.241.163/semdweb/InternetSOMD/ASP/1503540.asp). On the other hand, Stedman's confirms Aruffo's characterization of CD40 as being "present on mature B cells, monocytes, dendritic cells, and epithelial cells."

The significance of the fact that CD19, CD20 and CD22 are antigens that (i) have B cell lineage as the main reactivity, and (ii) have no reactivity with the gp39 ligand for CD40, is that there would have been no motivation to substitute an antibody to one of these 3 antigens for an antibody to CD40 as taught by Aruffo *et al.* The mechanism underlying Aruffo's invention relates to a blocking of the interaction between CD40 and its cognate ligand, gp39. The interaction between CD40 and gp39 "primes B cells to respond to subsequent stimulatory signals leading to B cell proliferation, differentiation and isotype switching" (Kiener *et al.*, *J. Immunol.* (1995)) and relates to "T cell-dependent B cell activation" (Foy *et al.*, *J. Exp. Med* (1993)). See also, product information for anti-mouse CD154 ("gp39 is expressed transiently by activated T cells...gp39 interaction with CD40 transduces signals for T-dependent B-cell activation" -- http://www.ebioscience.com/ebioscience/specs/antibody_16/16-1541. An antibody to CD19, CD20 or CD22 would not prevent interaction between CD40 and gp39, the function of the Aruffo antibody, and thus a person of skill in the art would have no reason to substitute one of these antibodies for the Aruffo anti-CD40 antibody.

The examiner cites portions of Aruffo *et al.* that suggest that B cells are transiently depleted. This is a secondary finding and is listed with "drug-related clinical observations,

changes in body weight and food consumption or alterations in hematology or serum Ig levels in any animal. The only drug-related findings observed were transient 70% and 43% decreases in the percentages of peripheral B cells with mAbs 2.36 and 2.220. Recovery of B cells to normal levels occurred within 2-3 weeks post-treatment." Thus, the transient B cell depletion is listed with adverse side effects of Aruffo's therapy. Aruffo *et al.* does not, as alleged by the examiner, "clearly appreciate the effect of anti-CD40 antibody on both direct reduction of B cell numbers and on inhibition of the B cell:T cell interaction that leads to amplification of the humoral immune response." Both mAb 2.36 and 2.220 led to a transient reduction in peripheral B cells, with the former causing almost twice the reduction of the latter. Yet the former was rejected by Aruffo because it did not significantly suppress antibody response upon subsequent immunization with SRBC (column 9, lines 46-51).

The result sought by Aruffo is a blocking of the interaction between CD40 and gp39 ("a key functional property for the desired anti-CD40 mAb was the capacity to completely block the interaction of CD40 and its ligand, gp39" - column 7, lines 21-24), leading to significant suppression of antibody response. To this end, Aruffo utilized various assay formats to select antibody candidates for further testing. From ***200*** initial candidates (column 7, lines 19-20), the field was limited to two for testing *in vivo* (column 8, lines 50-53). While both of these produced a transient reduction in peripheral B cell levels, ***only one of them, 2.220, significantly suppressed antibody response.*** The other candidate, 2.36 did not meet Aruffo's purpose. The clear message to be taken from Aruffo is that the ability to block interaction between CD40 and gp39 is a necessary, but not sufficient, basis for success in the ability to suppress antibody response and hence serve as a therapy in autoimmune diseases. It would not have been obvious that an antibody to CD19, CD20 or CD22 could be substituted for the anti-CD40 antibody of Aruffo, especially given that only one antibody in 200 was deemed by Aruffo to achieve the stated purpose of Aruffo's method.

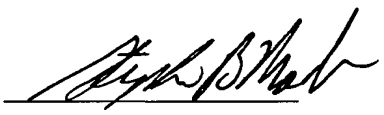
The basis for substituting and/or combining features from one or more of the secondary references is that ***CD40 is a B cell antigen like CD19, CD20 or CD22***. Thus,

for example, the examiner states that "Meyer *et al.* teach that in order to effectively regulate B cell responses *in vivo*, antibodies to ***multiple B cell surface antigens*** should be combined. Anderson *et al.* and Tedder *et al.* teach naked (*i.e.*, unconjugated) antibodies to CD20 and CD22 that can each be used to regulate ***B cell responses in vivo***." As explained above, Aruffo *et al.* teaches that CD40's characterization as a "B cell antigen" has been superceded by more recent recognition of its presence on a variety of cell types. As shown by the extensive evidence submitted with the response and discussed above, clearly CD40 is not a B cell antigen like CD22, CD20 and CD19, each of which has B cell lineage as the only or primary reactivity type. Accordingly, it would not have been obvious to substitute an antibody to one of the B cell antigens disclosed in Anderson *et al.*, Meyer *et al.* or Tedder *et al.* for an antibody to the CD40 antigen in Aruffo *et al.* No *prima facie* case of obviousness exists.

In view of the foregoing remarks, all claims are believed to be in condition for allowance. Should the examiner require anything further, she is invited to contact the undersigned at the local exchange provided below.

Respectfully submitted,

Date July 7, 2003

By 

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